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AF/ 1651

Attorney Docket No. 5405-223IPDV PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Opara
Serial No.: 10/054,796
Filed: January 23, 2002
For: *METHODS OF ENCAPSULATING CELLS*

Confirmation No.: 4935
Group Art Unit: 1651
Examiner: David M. Naff

March 22, 2004

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TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION--37 C.F.R. § 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF for the above-identified application, pursuant to the Notice of Appeal filed on January 20, 2004 and recited by the United States Patent and Trademark Office on January 23, 2004.

2. This application is filed on behalf of
☒ a small entity.

3. Pursuant to 37 C.F.R. § 1.17(c), the fee for filing the Appeal Brief is:
☒ small entity $165.00
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Appeal Brief fee due $165.00

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Susan E. Freedman

Susan E. Freedman
Date of Signature: March 22, 2004

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APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is filed in triplicate pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed on January 20, 2004 and received by the United States Patent and Trademark Office on January 23, 2004.

REAL PARTY IN INTEREST

The real party in interest is Duke University of Durham, North Carolina, the assignee of the rights to this application by virtue of assignment from the inventor recorded at the United States Patent and Trademark Office on April 14, 2000 on Reel 010752, Frame 0840.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no appeals or interferences that would be affected by the present appeal.

STATUS OF CLAIMS

Claims 6-13, 77 and 84-86 are pending in the present application as of the filing date of this Appeal Brief. Appellant appeals the final rejection of claims 6-13, 77 and 84-86. As of the filing date of this Appeal Brief, claims 6-13, 77 and 84-86 remain rejected under 35

U.S.C. § 103(a). A copy of claims 6-13, 77 and 84-86 is attached hereto as an appendix **(Appendix)** presenting the claims at issue as finally rejected in the Final Official Action dated December 4, 2003.

STATUS OF AMENDMENTS

A Response to Official Action was filed on September 16, 2003 responsive to the Official Action dated July 1, 2003. The Response to Official Action added new claims 85 and 86 which were acknowledged and entered in the Final Official Action. Accordingly, all amendments made by Appellant prior to submission of the present Appeal Brief are believed to have been entered.

SUMMARY OF THE INVENTION

Glycemic control in diabetes has been shown to delay the onset of, and slow the progression of, associated pathological complications. However, achieving adequate glycemic control using insulin therapy can be difficult. One alternative to insulin therapy is the transplantation of functioning pancreatic islet cells to diabetic subjects, to provide biological insulin replacement. However, transplanted or grafted islet cells encounter immunological rejection, which can limit the clinical usefulness of this method. *See* Present Application, pages 1-2. Microencapsulation of islet cells has been proposed to reduce or avoid immunological rejection of transplanted islet cells. The success of microencapsulated islet cell transplantation in treating diabetes depends on the ability of the microcapsules to provide sufficient amounts of insulin in response to glucose stimulation, over an extended period of time, to achieve adequate glycemic control. *See* Present Application, page 2.

Embodiments of the present invention, as recited in claims 6-13, 77 and 84-86, generally relate to biocompatible microcapsules that contain living cells. In some embodiments, the present invention provides microencapsulated cell products prepared by methods wherein cells are microencapsulated in a biocompatible microcapsule that contains a hydrogel core and a semipermeable outer membrane, to provide a microcapsule containing living cells therein. *See* Present Application, page 2. The microencapsulated cells can be incubated with a physiologically acceptable salt such as sodium sulfate or the like in order to produce a more durable, and therefore useful, biocompatible microcapsule. *See* Present Application, page 3. Cultures of isolated islet cells prior to encapsulation, cultures of

encapsulated cells, and cryopreservation of islet cells prior to encapsulation, are further provided.

ISSUE

Whether claims 6-13, 77 and 84-86 are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 5,821,121 to Brothers in further view of U.S. Patent No. 5,071,741 to Brockbank or Hamaguchi et al. *Diabetes Res. Clin. Pract.* **2**:337–345 (1986) or Garfinkel et al. *J. Surg. Res.* **76**:7–10 (1998) each taken with Janjic et al. *Pancreas* **13:**166–172 (1996) or Littman et al. *J. Surg. Res.* **59**:694-698 (1995) or Garfinkel et al. *FASEB J.* H:A436 #2520 (1997).

GROUPING OF CLAIMS

For the purposes of this Appeal with respect to the outstanding obviousness rejection, the claims may be grouped together as follows:

Group I: Claims 6-13 and 77;

Group II: Claim 84; and

Group III: Claims 85 and 86.

The claims of Group I stand or fall together, the claims of Group II stand or fall together and the claims of Group III stand or fall together.

ARGUMENT

I. Legal Standard of Obviousness

Appellant notes that a determination under 35 U.S.C. §103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. The Patent Office has the initial burden under §103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations of the present invention. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See Manual of Patent Examining Procedure* (M.P.E.P.) § 2143.

In the present case, the Examiner has not established a *prima facie* case of obviousness because the cited references fail to disclose or suggest all the claim recitations of the present invention, the combination of cited reference teachings fails to enable one of ordinary skill in the art to arrive at the claimed invention, and consequently, the cited references fail to provide a reasonable expectation of success.

II. The Rejection

In the Final Official Action dated December 4, 2003 (the Final Action), claims 6-13, 77 and 84-86 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,821,121 to Brothers (Brothers) in further view of U.S. Patent No. 5,071,741 to Brockbank (Brockbank) or Hamaguchi et al. *Diabetes Res. Clin. Pract.* **2**:337–345 (1986) (Hamaguchi et al.) or Garfinkel et al. *J. Surg. Res.* **76**:7–10 (1998) (Garfinkel (1998)) each taken with Janjic et al. *Pancreas* **13:**166–172 (1996) (Janjic et al.) or Littman et al. *J. Surg. Res.* **59**:694-698 (1995) (Littman et al.) or Garfinkel et al. *FASEB J.* H:A436 # 2520 (1997) (Garfinkel (1997)). The Examiner states the following:

> [i]t would have been obvious to carry out the encapsulation of pancreatic islet cells as suggested by Brothers by microencapsulating the cells to obtain the function of microencapsulating the pancreatic islets for transplantation as taught by Brockbank, Hamaguchi et al. or Garfinkel et al. (document 266) when microencapsulating pancreatic islets for transplantation. Janjic et al., Littman et al. or Garfinkel et al. (document 265) would have suggested that glutathione in the medium of Brothers will function to enhance insulin secretion by the pancreatic islets. The resulting cultured microencapsulated cells would have inherently had a weight gain and basal insulin secretion as presently claimed. The medium of Brothers contains salts (column 49, line 29), and after encapsulating it would have been obvious to culture the islet cells in this medium. The salts would have inherently increased durability of the microcapsules.

Final Action, page 4, first paragraph.

Appellant respectfully submits that the claims of Group I (claims 6-13 and 77), Group II (claim 84) and Group III (claims 85 and 86) are not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request reversal of the rejection of claims 6-13, 77 and 84-86 for reasons provided below.

III. Claims 6-13 and 77 Are Not Obvious Under 35 U.S.C. § 103(a) In View of The Cited References

A. The Cited References Do Not Teach or Suggest The Products Recited in Claims 6-13 and 77

Claim 77 is directed to microencapsulated islet cell products comprising microcapsules containing isolated living pancreatic islet cells therein, said microencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month.

In contrast, none of the cited references teach or suggest a microencapsulated islet cell product as recited in the claims of the present application. More specifically, **Brothers** describes methods for establishing and maintaining pancreatic islet cells in long-term cell culture in a medium containing glutathione and merely suggests that these cells may be encapsulated for implantation.

Brockbank merely describes a novel class of nonpermeating cryoprotectants which, when mixed with certain known permeating cryoprotectants, provide a medium for protection of living cells during a routine cryopreservation process.

Hamaguchi et al. merely describes a general technique for microencapsulating pancreatic islet cells and its general application to culture and transplantation.

Garfinkel et al. (1998) merely describes a process of chelation of microencapsulated islets with, for example, sodium citrate that appears to be essential for optimal function (insulin secretion upon glucose challenge) of said islets.

Janjic et al. merely proposes that the glutathione redox state (GSH/GSSG) in human islet cells decreases after cryopreservation and that insulin secretion of cryopreserved human islet cells can be improved by treatment with antioxidants (BHA).

Littman et al. merely describes that incubating isolated islets with glutathione preserved and enhanced islet function.

Finally, **Garfinkel et al. (1997)** merely proposes that porcine islets that are pre-treated with glutathione enhance pancreatic islet function in vitro.

Clearly, these references **do not** teach or suggest microencapsulated islet cell products comprising microcapsules containing isolated living pancreatic islet cells therein, said microencapsulated islet cells **exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month**. In view of the deficiencies of the cited references, even if combined, the cited references would not provide all the claim recitations directed to microencapsulated islet cell products as recited in claim 77. Consequently, the cited references do not teach or suggest the products recited in independent claim 77 or the products claimed in dependent claims 6-13.

B. The Resulting Microencapsulated Cells Disclosed in the Cited References Would Not Have Inherently Had a Weight Gain and Basal Insulin Secretion as Presently Claimed

Appellant respectfully disagrees with the assertion in the Final Action that a microencapsulated cell product prepared according to the teachings of the cited references would have inherently had a weight gain and basal insulin secretion as is claimed in the rejected claims. It is stated in § 2112 of the M.P.E.P. that the Examiner must provide rationale or show evidence tending to show inherency. *In re Robertson,* 49 U.S.P.Q.2d 1949, 1950–51 (Fed. Cir. 1999) states that:

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probability or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"

The Final Action provides no support for the assertion that a microencapsulated cell product prepared according to the teachings of the cited references would inherently have a weight gain and basal insulin secretion as is claimed in the present invention.

One of the concerns with polylysine alginate microencapsulated cells is their durability, in particular with microcapsules that have been chelated (Lines 11–13, second paragraph of the introduction, Garfinkel et al. (1998)). Furthermore, the concerns of the long-term durability of microencapsulated islets are related in part to bead swelling, which results in disintegration of capsules due to colloid osmotic pressure induced by residual Ca^{++} after chelation of the microcapsules with sodium citrate in a manner as taught by Garfinkel et al. (1998). **Microcapsules prepared in this manner increased in diameter by 20% in 9 days, followed by disintegration or became nonspherical. Thus, microencapsulated cells and products thereof do not inherently have the characteristics of weight gain and basal insulin secretion of the present invention.** However, no significant increase in size for up to 34 days was observed in microcapsules that are subsequently incubated with a physiologically acceptable salt, for example sodium sulfate, as is outlined in the data presented in Figures 5 and 6 of the present application. Thus, the resulting microencapsulated cell products provided by the cited references do not "inherently" exhibit weight gain and basal insulin secretion as is claimed in the present application.

Accordingly, Appellant respectfully submits that claims 6-13 and 77 are not obvious under 35 U.S.C. § 103(a) in view of Brothers in further view of Brockbank, or Hamaguchi et al. or Garfinkel (1998) each taken with Janjic et al. or Littman et al. or Garfinkel (1997), and respectfully request reversal of the rejection of claims 6-13 and 77.

IV. Claim 84 Is Not Obvious Under 35 U.S.C. § 103(a) In View of The Cited References

For reasons set forth above in Section III, Appellant respectfully submits that the subject matter of claim 84 is not obvious in view of the cited references. Moreover, Appellant notes that claim 84 recites as follows:

84. A microencapsulated islet cell product comprising microcapsules containing isolated living pancreatic islet cells therein, said microencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month;

wherein said microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane;

and wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

Thus, claim 84 sets forth additional recitations directed to the microcapsule wherein the microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane and also has a diameter of from about 300 μm to about 700 μm. The cited references do not teach or suggest microencapsulated islet cell products as recited in claim 84. In fact, the cited references fail to provide **any** teachings regarding the microcapsule comprising a specific membrane surrounding such as polysaccharide gum surrounded by a semipermeable membrane and a specific diameter such as one from about 300 μm to about 700 μm.

Accordingly, Appellant respectfully submits that claim 84 is not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request reversal of the rejection of claim 84.

V. Claims 85 and 86 Are Not Obvious Under 35 U.S.C. § 103(a) In View of The Cited References

For reasons set forth above in Section III, Appellant respectfully submits that claims 85 and 86 are not obvious in view of the cited references. Additionally, Appellant notes that claims 85 and 86 further recite that the microencapsulated islet cell can be produced by the process of incubating the microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule. The cited references do not teach or suggest a process of incubating the microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule. However, the Final Action states that "[t]he medium of Brothers contains salts (column 49, line 29) . . . . The salts would have inherently increased durabilility of the microcapsules. Final Action, page 4, first paragraph.

It is reiterated that in order to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *See In re Robertson*, 49 U.S.P.Q.2d 1949 at 1950–51. Additionally inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Id.* at 1950–51.

In this instance, the Examiner merely asserts that the salts would have inherently increased durability of the microcapsules. The Examiner has not provided a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent

characteristic necessarily flows from the teachings of the cited reference. *See Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The information that is available shows that microcapsules prepared according to processes described in the cited references increased in diameter by 20% in 9 days, followed by disintegration or became nonspherical. In stark contrast, no significant increase in size for up to 34 days was observed in microcapsules that are subsequently incubated with a physiologically acceptable salt as recited in the claims of the present invention. *See* Section III.B. above.

Where the cited references fail to describe a process of incubating the microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule, the cited references fail to teach or suggest the products recited in claims 85 and 86. Additionally, the mere mention of "salts" in the medium **does not** cure the deficient teachings of the cited references.

Accordingly, Appellant respectfully submits that claims 85 and 86 are not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request reversal of the rejection of claims 85 and 86.

In summary, the cited references, in combination, are generally directed to microencapsulation of islet cells. However, these general teachings **do not** enable one of ordinary skill in the art to arrive at the following:

(a) microencapsulated islet cell products comprising microcapsules containing isolated living pancreatic islet cells therein, said microencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month as recited in claim 77;

(b) microencapsulated islet cell products comprising, among other things, a polysaccharide gum surrounded by a semipermeable membrane and having a diameter of from about 300 μm to about 700 μm as recited in claim 84; and

(c) microencapsulated islet cell products produced by the process of incubating the microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule as recited in claims 85 and 86.

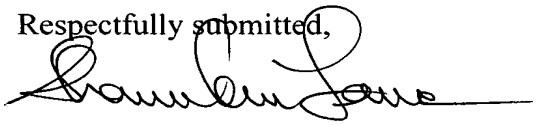
For reasons set forth above, Appellant respectfully concludes that the Examiner has not established a *prima facie* case of obviousness because the cited references fail to disclose all the claim recitations of the present invention, the combination of cited reference teachings fails to enable one of ordinary skill in the art to arrive at the claimed invention, and consequently, the cited references fail to provide a reasonable expectation of success.

Accordingly, Appellant respectfully submits that Group I claims (claims 6-13 and 77), Group II claim (claim 84) and Group III claims (claims 85 and 86) are not obvious in view of Brothers in further view of Brockbank, or Hamaguchi et al. or Garfinkel (1998) each taken with Janjic et al. or Littman et al. or Garfinkel (1997).

CONCLUSION

In light of the entire record and the above discussion, Appellant respectfully submits that claims 6-13, 77 and 84-86 are patentable over the cited references. Accordingly, Appellant respectfully requests reversal of the pending rejection of claims 6-13, 77 and 84-86 and that this case be passed to issuance.

Respectfully submitted,



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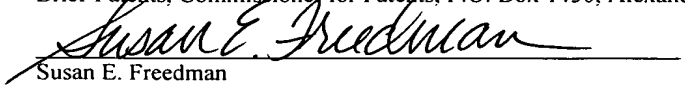

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Date of Signature: March 22, 2004

TABLE OF AUTHORITIES

CASES

STATUTES

OTHER AUTHORITIES

APPENDIX

What is Claimed is:

1-5. (Canceled)

6. (Previously Presented) A product according to claim 77, where said microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane.

7. (Previously Presented) A product according to claim 77, where said microcapsule comprises alginate in combination with polylysine, polyornithine, and combinations thereof.

8. (Previously Presented) A product according to claim 77, wherein said microcapsule has an internal cell-containing core of alginate.

9. (Previously Presented) A product according to claim 8 wherein said internal cell-containing core of alginate is gelled.

10. (Previously Presented) A product according to claim 77, wherein said internal cell-containing core of alginate is not gelled.

11. (Previously Presented) A product according to claim 77, wherein said microcapsule has a diameter of from about 50 μm to about 2 mm.

12. (Previously Presented) A product according to claim 77, wherein said microcapsule has a diameter of from about 200 μm to about 1000 μm.

13. (Previously Presented) A product according to claim 77, wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

14-76. (Canceled)

77. (Previously Presented) A microencapsulated islet cell product comprising microcapsules containing isolated living pancreatic islet cells therein, said microcencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month.

78-83. (Canceled)

84. (Previously Presented) A microencapsulated islet cell product comprising microcapsules containing isolated living pancreatic islet cells therein, said microcencapsulated islet cells exhibiting a weight gain of not more than 10 percent by weight over a period of one month in physiological saline solution at 37 degrees Celsius and exhibiting at least 150 percent basal insulin secretion in response to 16.7 milliMolar glucose challenge in Krebs-Ringer physiological solution at pH 7.4 after said period of one month;

wherein said microcapsule comprises a polysaccharide gum surrounded by a semipermeable membrane;

and wherein said microcapsule has a diameter of from about 300 μm to about 700 μm.

85. (Previously Presented) A microencapsulated islet cell product according to claim 77, wherein said microencapsulated islet cell is produced by the process of incubating said microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule.

86. (Previously Presented) A microencapsulated islet cell product according to claim 84, wherein said microencapsulated islet cell is produced by the process of incubating said microcapsule following microencapsulation with a physiologically acceptable salt to increase the durability of the microcapsule.